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# TO COMPARE THE SEDATION AND ANALGESIA PRODUCED BY CONTINUOUS INFUSIONS OF DEXMEDITOMIDINE AND BUTORPHANOL IN CRITICALLY ILL PATIENTS ON MECHANICAL VENTILATION: A RANDOMIZED DOUBLE BLIND CONTROLLED TRIAL.

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**ABSTRACT**

**BACKGROUND:** Sedation in intensive care unit for critically ill patients on mechanical ventilation is a complex clinical problem and the current therapeutic approaches have potential side effects. This study was aimed at comparing inj. dexmedetomidine with inj. butorphanol as sedative and analgesic, their untoward effects, whether their use reduces the requirement of rescue sedative and analgesic agents and their cost effectiveness.

**METHODS:** 60 Patients of both sexes in the age group of 20-60 yrs requiring mechanical ventilation for postoperative (major laparotomy surgeries) indications were included in the study. Once the patient was put on mechanical ventilation, the infusion of specified drug was started using syringe pump. Dexmedetomidine was started at the rate of 0.7 µgm/kg/ hr and butorphanol was started at the rate of 5 µgm /kg/hr depending upon the parameters of assessment and requirement of the patient. Infusion was continued for 24hrs or until weaning off from the ventilator which ever was less. Vital parameters, Glasgow Coma Score, Sedation score (Brussels's Sedation score), agitation during weaning and after extubation and nausea vomiting were compared.

**RESULTS:** The patients receiving dexmedetomidine infusion were haemodynamically more stable and were easily arousable while he patients receiving butorphanol infusion were more drowsy with acceptable, but lower respiratory rates.

**CONCLUSION:** Dexmedetomidine is a suitable alternative to the commonly used sedatives in ICU, but its high cost may limit its use in the initial phase.

**KEYWORDS :** Butorphanol, dexmeditomidine, ICU, mechanical ventilation, sedation

## INTRODUCTION

Sedation in ICU for critically ill patients on mechanical ventilation is a complex clinical challenge and current therapeutic approaches have potential side effects[1]. Improper or inadequate sedation and analgesia in such patients causes agitation. Major causes of agitation in ICU patients are fear, loss of control, confusion, sleep deprivation, pain, chemical imbalances, medication, and mechanical ventilation [2]. Agitated patients are often hypertensive, have increased stress hormones and require more intense nursing care [1]. Hence to reduce agitation it is essential that the used therapeutic approach should provide sufficient analgesia and sedation for such patients.

A continuous infusion of sedatives is found to be an independent predictor of longer duration of mechanical ventilation as well as longer stay in ICU[3, 4]. This study was conducted to look for a novel sedative and analgesic for mechanically ventilated patients in ICU that does not have undesirable autonomic effects, agitation, any residual effects and also that is cost effective. Our primary aim was to compare Dexmedetomidine and Butorphanol for their analgesic and sedative efficacy in mechanically ventilated patients and secondary aim was to look for side effects and cost effectiveness of these drugs.

Dexmedetomidine is a short acting alpha 2 agonist with anxiolytic, anaesthetic, hypnotic and analgesic properties[5]. Its popularity is due to its ability to produce co-operative sedation [6]. It was approved for its use in 1999[7]. Its use in humans was approved for short term medication (<24 hrs) for sedation and analgesia in ICU [8]. Dexmedetomidine has a neuroprotective action. It decreases the peripheral catecholamines, thus balancing the ratio between oxygen supply, reduces excitotoxicity, and improves the perfusion in the ischemic penumbra[9].

Butorphanol is a synthetic opioid analgesic. It has a significantly longer duration of action. It exhibits partial agonist antagonist activity at µ receptor and agonist at kappa receptors[10]. As with all opioid drugs it causes sedation, nausea and vomiting. In terms of cost, it is very economical, which is an added advantage.

There have been limited studies designed specifically to evaluate the efficacy of dexmedetomidine and nearly no studies investigating butorphanol for sedation and analgesia in mechanically ventilated patients. Butorphanol was being used routinely as sedative and analgesic in intermittent doses (1mg every 4 hourly) for mechanically ventilated patients in the ICU of our institute. Hence we decided to compare these two less investigated but promising drugs.

## METHODOLOGY:

After obtaining institutional ethical committee clearance, 60 patients in age group of 20-60 years, who needed mechanical ventilation for post operative indications, were included in the study. The study was designed to be randomized, prospective and double blind. Randomization was done using computer generated random sequence and allocation concealment was ensured using sequentially- numbered opaque, sealed envelopes. Patients were allocated to two groups randomly by a computer generated list. As soon as the patient was shifted to the ICU on ventilator, vital parameters were noted and infusion of the group specific drug was started using the syringe pump. Group A patients received Inj. Dexmedetomidine at the rate of 0.7mcg/kg/hr and Group B patients received Inj. Butorphanol at the rate of 5mcg/kg/hr. Rescue sedation that is propofol 1mg/kg was started as and when required, while monitoring heart rate, blood pressure, peak airway pressure and trigger on the ventilator. We deployed Maquet Servo S ventilators, uniformly to all the patients. The post operative assessment was carried out by an anaesthesiologist/ intensivist who was unaware of the drug that was being infused. Vital parameters were noted at regular intervals. Duration for the first dose of rescue sedation and the time interval between the requirements of rescue sedation were noted and after extubation the total required dose of rescue sedation was also calculated. Assessment of patient's status using Glasgow Coma Score and Brussels' sedation scale were noted the next early morning when the infusions were discontinued and patients were given a trial of weaning from the ventilator. Vital parameters and any untoward effects of the drugs were noted after extubation. Infusion of the drug was continued until weaning off of the patient from the ventilator or for 24 hours which ever was less. Patients who needed ventilation for more than 24 hours were automatically excluded from the study.

## RESULTS

### Statistical Analysis

Statistical analysis was done using SPSS 11.5™ software. Data was presented as mean ± standard deviation. A p value of > 0.05 was considered as statistically significant.

Demographically there was no difference in the two groups. Before starting the infusion there was a significant difference in the pulse rate of the two groups, which was confirmed statistically but was not clinically significant (Table 1).

**Table 1: Comparison of pulse rate in study groups**

| Pulse Rate (min) | Group A Mean ± SD (n=10) | Group B Mean ± SD (n=10) | t- Value | P Value |
|---|---|---|---|---|
| T0 | 82.4 ± 7.27 | 92.6 ± 10.29 | 2.56 | <0.05 |
| T1 | 67.9 ± 9.31 | 75.4 ± 7.06 | 2.03 | >0.05 |
| T2 | 83.5 ± 16.45 | 95.5 ± 9.92 | 1.97 | >0.05 |

The patients in group A showed a higher systolic blood pressure before starting the infusion which was not clinically significant. Contrary to the usual belief, there was no significant difference in the systolic and diastolic blood pressure, percentage saturation of oxygen ($SpO_2$) in group A and B.

The most important findings which we could derive were the significant difference in the time interval between the rescue sedative doses and the total requirement of rescue sedation in study groups. This time interval was nearly double in group A, hence the requirement of rescue sedation was nearly half in this group, and both of the findings were statistically highly significant, suggesting an excellent quality of sedation and analgesia. (Tables 2 and 3, Figures 1 and 2).

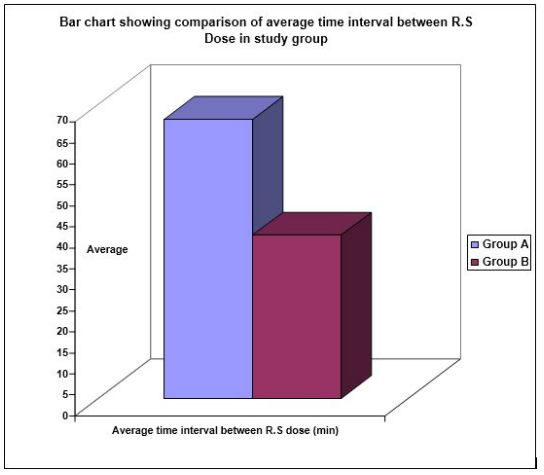
**Table 2: Comparison of average time interval between rescue sedative dose in study groups**

| Time interval between | Group A | Group B | t- Value | P Value |
|---|---|---|---|---|
| | Mean ± SD (n=10) | Mean ± SD (n=10) | | |
| R.S dose (min) | 66.5 ± 13.13 | 39 ± 6.58 | 5.92 | <0.0001 |

**Table 3: Comparison of Total requirement of propofol in study groups**

| Total requirement | Group A | Group B | t- Value | P Value |
|---|---|---|---|---|
| | Mean ± SD (n=7) | Mean ± SD (n=7) | | |
| of R.S (mg) | 12.7 ± 2.36 | 25.4 ± 5.19 | 7.04 | <0.0001 |

**Figure 1**



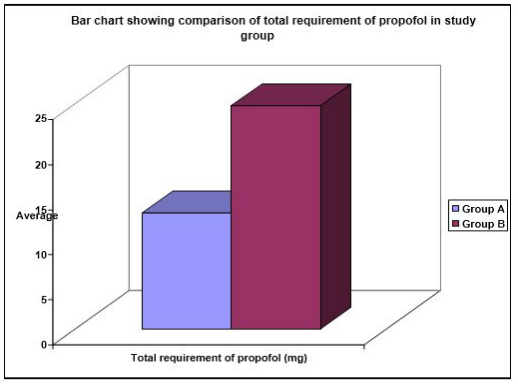




**Figure 2. Comparison of total requirement of Propofol in study groups**

The mean duration between discontinuation of drug infusion and extubation were 20min+/- 10 and 40min+/- 10 respectively.

Respiratory rate during weaning and after extubation was significantly low in butorphanol group patients suggesting some amount of respiratory depression by Butorphanol, it being an opioid drug (Table 4, Figure 3).

**Table 4: Comparison of respiratory rate in study groups**

| RR | Group A | Group B | t- Value | P Value |
|---|---|---|---|---|
| | Mean ± SD (n=7) | Mean ± SD (n=7) | | |
| T0 | 13.00 ± 0.82 | 14 ± 1.63 | 1.73 | >0.05 |
| T1 | 15 ± 0 | 15 ± 0 | 0 | >0.05 |
| T2 | 15.1 ± 0.87 | 11.2 ± 0.79 | 10.46 | <0.0001 |

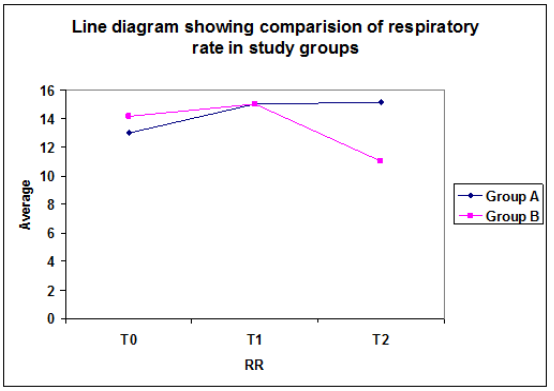



**Figure 3. Comparison of respiratory rate in study groups**

The Glasgow Coma Scores in both the groups was almost equal and near to 15 while and Brussel's Sedation scores did not show any significant difference suggesting there was no residual sedation or CNS depression (0.4 ± 0.52 in dexmedetomidine group, while 0.8 ± 0.79, p value >0.05).

Few patients in Butorphanol group complained of vomiting during weaning and after extubation where as there was no such complaint in patients of Dexmeditomidine group (Table 5).

**Table 5: Comparison of Nausea / vomiting in study groups**

| Parameters | Group A (n=10) | Group B (n=10) | Z- Value | P Value |
|---|---|---|---|---|
| Nausea / vomiting | 0 (0) | 6 (60) | 3.87 | <0.001 |

There is a significant difference in the effective cost of both groups. Butorphanol is more cost effective than Dexmeditomidine (Table 6).

**Table 6: Comparison of cost in study groups**

| Parameters | Group A | Group B | t- Value | P Value |
|---|---|---|---|---|
| | Mean ± SD (n=10) | Mean ± SD (n=10) | | |
| Cost (Rs.) | 1170 ± 141.81 | 605 ± 134.27 | 9.15 | <0.0001 |

## DISCUSSION

For patients on mechanical ventilation, in ICU, appropriate sedation and analgesia is one of the key factors to ensure patient's comfort [11] and improve the outcome.

Over sedation can lead to prolonged duration of mechanical ventilation/ difficulty in weaning off, longer ICU stay etc [12]. Under sedation can lead to anxiety, hyperactivity of the sympathetic system, delirium etc[13].

We compared dexmedetomidine and butorphanol, as sole sedative and analgesic agents for mechanically ventilated patients and found out that both the drugs provided comparable and optimal conditions in the ventilated patients except for few but gross differences.

Inj. dexmedetomidine when infused in mechanically ventilated patients over a period of 16- 24 hours showed a gross reduction in the requirement of muscle relaxant drugs as compared with that of butorphanol infused patients. Butorphanol infusion also reduces the requirement of muscle relaxant, but not as effectively as dexmeditomidine. Trittscho AE et al also studied that dexmedetomidine reduced the requirement of concurrently administered sedative and analgesic, e.g. Propofol.

Our study showed that patients in both the groups, receiving dexmedetomidine infusion and butorphanol infusion remained haemodynamically stable. Hogue CW Jr. et al concluded in their study that dexmedetomidine blunts heart rate and systemic sympathetic

activation [14]. Ricker et al in 2009 also found that patients receiving dexmedetomidine had less delirium, tachycardia, and hypotension.

We also observed that there was some amount of respiratory depression in patients receiving Butorphanol infusion where as the patients on Dexmedetomidine infusion had their respiratory drives and ventilator responses preserved. This finding has also been studied by Dr. Ebert as mentioned in a special report on Dexmedetomidine[4].

Patients in both the groups showed a GCS score of around 14-15, suggesting that there was no CNS depression or residual sedation.

Patients receiving Butorphanol were drowsier as assessed by Brussels' sedation score which was not statistically significant; they needed about 30-60 minutes of time more to be weaned off from the ventilator. Such results were expected, as butorphanol being an opioid drug causes more sedation and suppression of respiratory drives.

Patients receiving dexmedetomidine showed no adverse effects where as 6 (66.6%) out of 10 patients receiving butorphanol infusion complained of nausea and vomiting.

We had certain limitations in our study. The limitation of use of dexmedetomidine is its cost. Even though the purchasing cost of dexmedetomidine might be higher, the net cost effectiveness due to decreased requirement of rescue sedation, the reduced ventilator stay, the consequent use of oxygen and electricity and total ICU stay may counter balance the initial cost.

## CONCLUSION

We conclude that dexmedetomidine has turned out to be an excellent sedative and analgesic agent without any significant adverse effects; which can be used as a sole agent for mechanically ventilated patients in ICU.

Butorphanol can also be used as a sole sedative and analgesic in ICU as it is cost effective and does reduce the requirement of rescue sedation to some extent. The adverse effects of respiratory depression and nausea, vomiting can be treated by oxygen supplementation and antiemetics (inj ondenstron 4mg intravenously) respectively.

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